REMARKS

Reconsideration and withdrawal of the restriction requirement and election of species is respectfully requested in view of the remarks herein.

The October 30, 2008 Office Action required restriction from among the following:

Group I: Claims 13-27 (all in part), drawn to a method for treatment or prevention of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising a D-proline of the Formula I-A; and,

Group II: Claims 13-27 (all in part), drawn to a method for treatment or prevention of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising a D-proline of the Formula I-B.

The Office Action further required a species election to a single species of D-proline of Formula I-A or I-B.

Applicants hereby elect, with traverse, the claims of Group I and the compound (R)-1-[6-[(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC). The elected compound reads on claim 26; all of claims 13-25 and 27 are generic.

The Office Action alleges that the claims of Groups I-II lack unity of invention because they do not relate to a single inventive concept under PCT Rule 13.2. In particular, the Office Action alleges that the claims of Groups I-II lack a "special technical feature" that defines a contribution over Askarov or Brion. PCT Rule 13.2 states that

> *"Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression* ***"special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.****"*
> (emphasis added).

Applicants hereby traverse the finding of a lack of a "special technical feature".

The claims of Groups I-II all recite the "technical feature" of the treatment or prevention of osteoarthritis comprises administering to the subject a therapeutically effective amount of a medicament comprising an agent capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma of the subject. This technical feature is not taught by either Askarov or Brion.

Askarov et al. allegedly relates to "treatment of osteoarthritis with heparin" and Brion allegedly relates to "treating osteoarthritis with chondroitin sulphate". The Office further alleges that "both heparin and chondroitin sulphate are know[n] to bind to SAP." Applicants respectfully disagree with this over-simplification.

The present claims specifically require administration of a medicament comprising an agent capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma. The Office Action fails to state, and the cited references fail to show, that either chondroitin sulphate or heparin are capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma, as is part of the special technical feature of the present invention.

Indeed, the use of chondroitin sulphates (CS) in the treatment of degenerative joint disease (i.e., at 800mg orally, twice daily; see page 67, 2nd column, 5th paragraph of Brion) is a traditional, conservative treatments acknowledged in the background section of the present application. What is not described in Brion. is that SAP is a therapeutic target or that the use of CS in any way interacts with SAP. CS is not capable of inhibiting SAP ligand binding *in vivo* or depleting SAP from the plasma of a subject *in vivo*. That is, CS is not bound by SAP with sufficient affinity or specificity, if indeed it is bound at all by SAP in whole plasma, to be effective *in vivo*. Nothing in the cited reference would provide concentrations of CS which would be effective to inhibit binding of SAP to ligands in vivo, as is required by the special technical feature.

Turning to Askarov, it is submitted here, and known to any competent medical practitioner, that heparin could only ever be used as a medicament at extremely low dosages in view of its known potent anticoagulant activity. Heparin is used clinically only as an anti-coagulant to prevent blood clotting (thrombosis) and its consequences, such as ischaemic necrosis of tissue and thromboembolism. Any individual receiving heparin other than at extremely low dose has profound inhibition of blood coagulation and is at greatly increased risk of dangerous or fatal hemorrhage, either spontaneously or caused by even minor trauma. The use of heparin as an agent to treat or provide symptomatic relief in osteoarthritis is thus completely inconceivable in actual clinical

practice. Also heparin, like CS, is not bound by SAP in plasma with sufficient affinity or specificity to be effective in modifying SAP function *in vivo.* In particular, heparin and its various fractions of different molecular weight are instantly bound with extremely high affinity and avidity by anti-thrombin III in plasma. This is the basis of its anti-coagulant activity. No heparin is therefore available to be bound by SAP.

Therefore, the pending claims do have a special technical feature and therefore do not lack unity.

Furthermore, the MPEP states that *"the decision with respect to unity of invention rests with the International Searching Authority or the International Preliminary Examining Authority."* MPEP §1850. As can be seen from the attached copy of the International Search Report (ISR) of the parent application (PCT/GB04/002445), the International Searching Authority did **not** find a lack of unity of invention (see ISR page 1, Box 3). Although the claims of the present invention are newly added (other than claim 13) from the PCT application, claims 14-27 serve only to rewrite the PCT claims in US format, and are similar in scope to those in the PCT application. That is, the claims differ only in respect to certain formalities, such as converting the claims from European style "use" claims to U.S. style "method" claims. The claims of the present application recite the same "special technical features" as recited in the claims of the parent PCT application. As such, there is no reason to justify disregarding the findings of the International Preliminary Examining Authority regarding unity of invention.

While it is normally justifiable for a U.S. Examiner to assert that the holding of an Examiner from a foreign office is of little probative value, this is so because the applicable rules for the respective countries are different. This is NOT the case with respect to lack of unity of invention, i.e. the same rules for unity of invention which apply to the present Examiner also applied to the Examiner of the PCT application and there has been no indication as to why the previous Examiner's decision was clearly erroneous. MPEP 706.04 strongly hints at the deference that is to be accorded to the findings by the previous patent examiner of an application – *"Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the mere hope of finding something."* *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 139, 57 USPQ2d 1449, 1499-50 (D. Mass.

2001)." Therefore, any holding of lack of unity of invention should have also included a statement as to why the previous Examiner's action was a clear error. This statement will not be necessary in the Examiner's reply should restriction requirement be withdrawn by the Examiner.

In summary, the claims of Groups I-II satisfy the unity of invention requirements of PCT Rule 13.2. Accordingly, reconsideration and withdrawal of the restriction requirement based on lack of unity under PCT Rule 13.2 is respectfully requested.

The Office Action further required an election of a single species of D-proline derivative on the basis that the claims allegedly lack a technical feature that makes a contribution over EP 0915088. Applicants respectfully disagree.

Again, the present claims specifically require administration of a medicament comprising an agent capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma, including wherein the agent is a compound of Formula I-A or I-B. That is, it is not sufficient to rely on a reference that may show D-prolines of Formula I-A or I-B; rather, such a reference would have to show such D-prolines used in a medicament for the treatment or prevention of osteoarthritis, wherein the compound is capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma. No such use is provided in EP 0915088, and the claims therefore have a special technical feature that provides a contribution over the art.

In summary, the compounds of Formula I-A and I-B satisfy the unity of invention requirements of PCT Rule 13.2. Accordingly, reconsideration and withdrawal of the restriction requirement based on lack of unity under PCT Rule 13.2 is respectfully requested.

In addition, enforcing the present restriction requirement and species election would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO, as well as extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional or continuing applications filed). Restriction has not been shown to be proper, especially since the requisite showings have not been made in the Office Action and there are relationships and special technical features between all of the pending claims. Indeed, the search and examination of each Group is likely to be co-extensive and, in any event, would involve such interrelated art such that the search and examination of the entire application can and should be made without. All of the foregoing, therefore, mitigate against restriction.

CONCLUSION

Reconsideration and withdrawal of the restriction requirement and election of species, and a favorable examination on the merits is respectfully requested in view of the remarks herein.

Respectfully submitted,
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